

FIG. 1

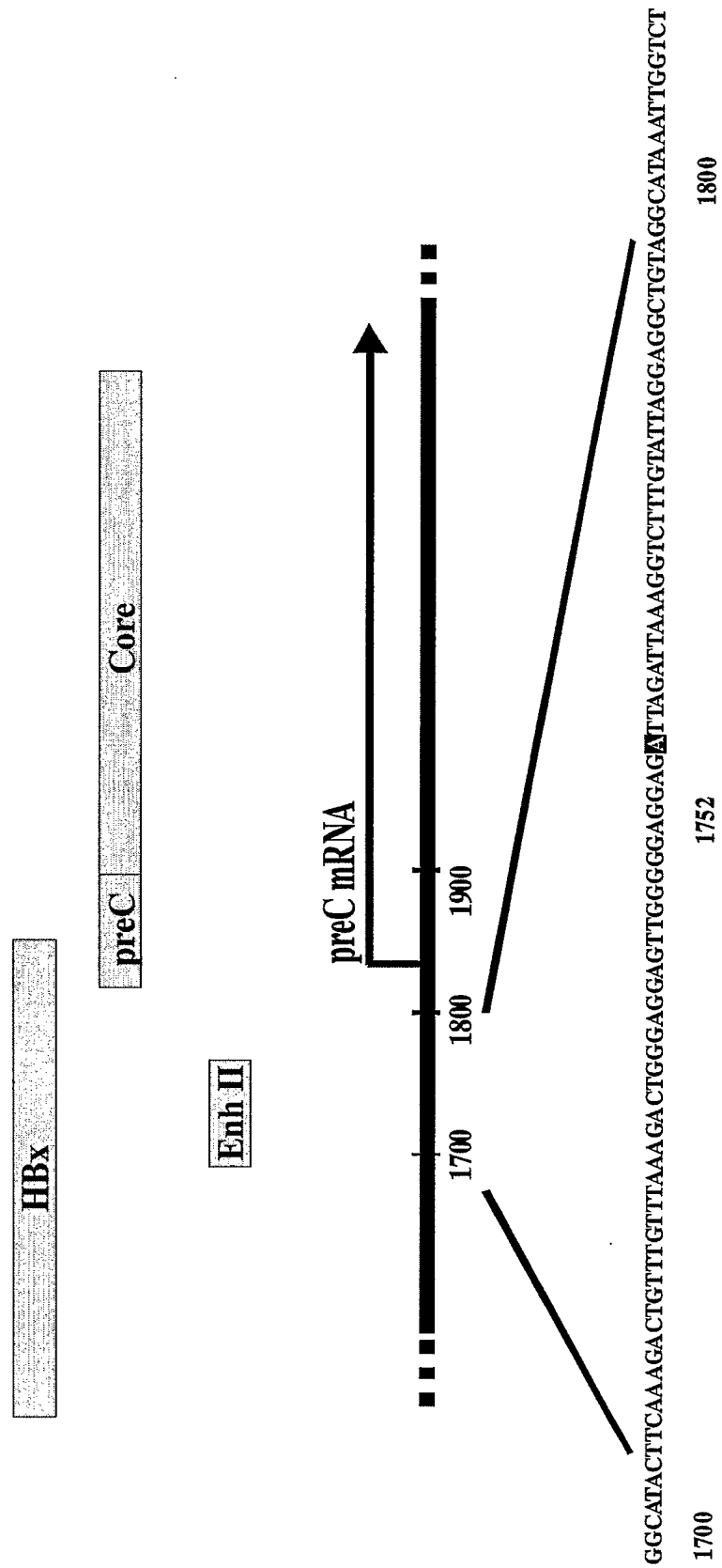
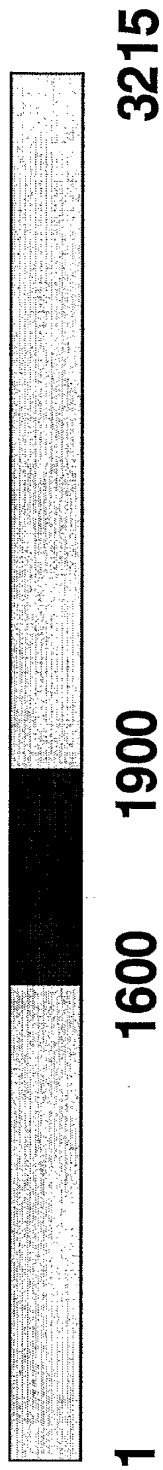
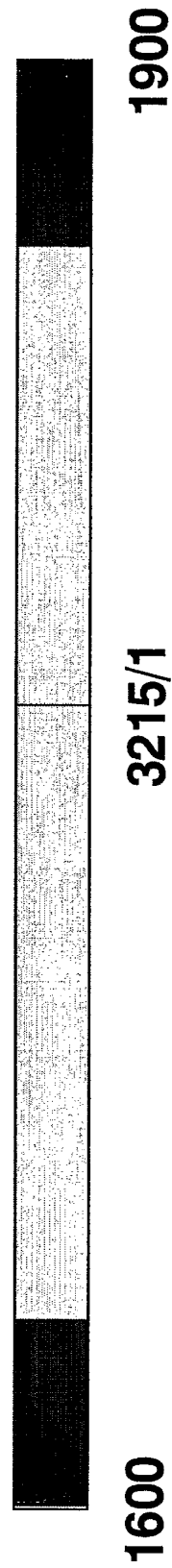


FIG. 2



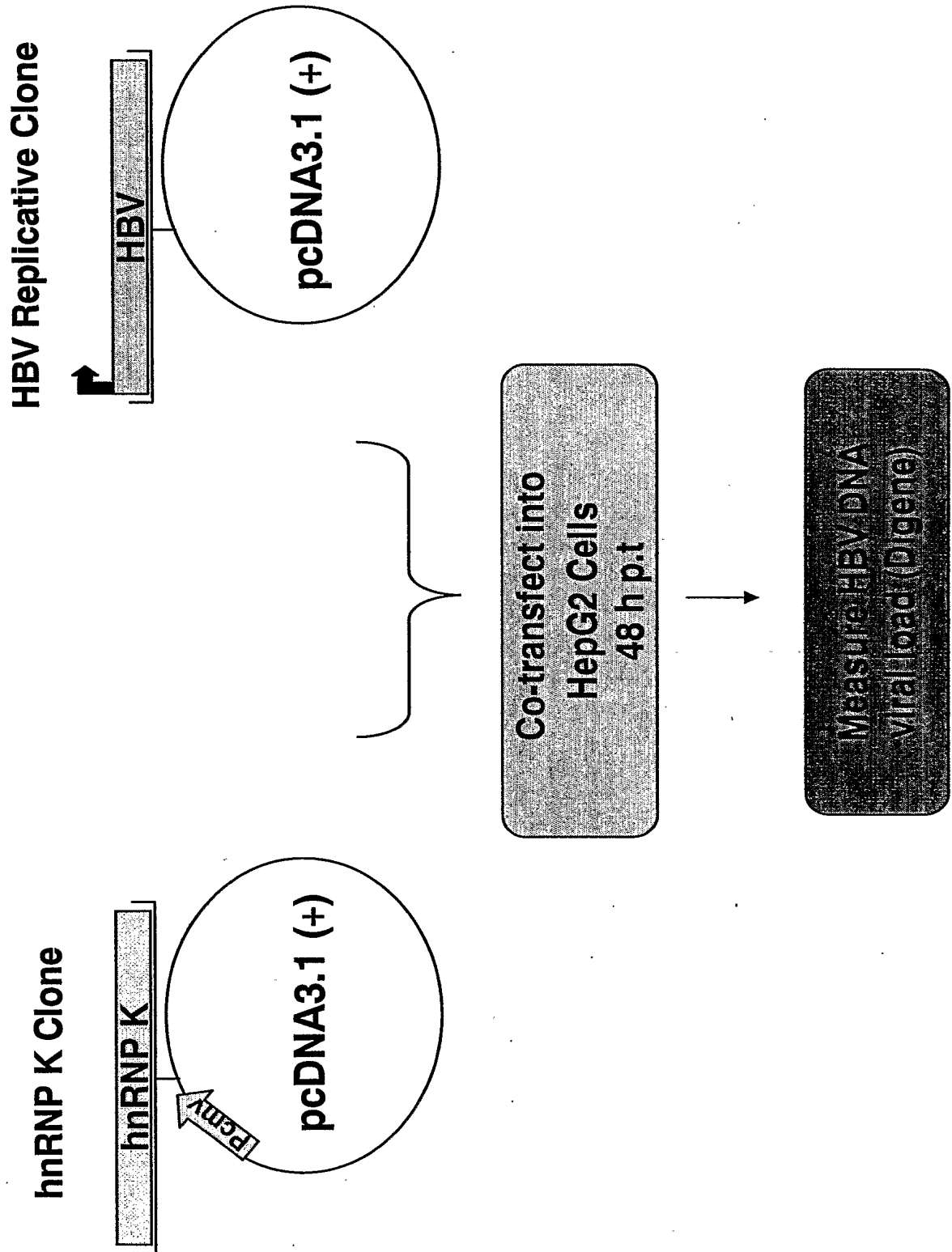
ATCC clone available in pBR325



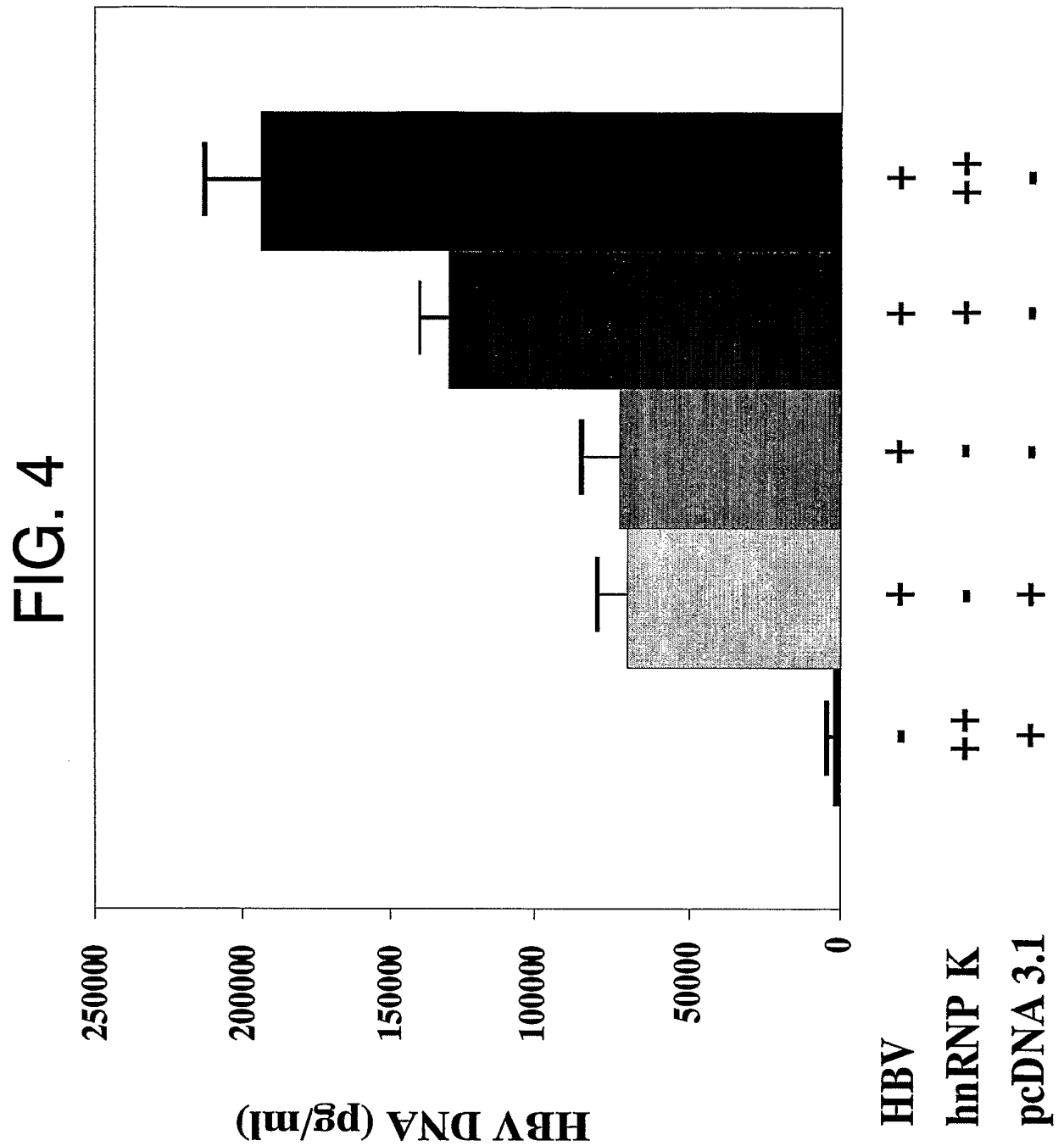
Replicative clone generated

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FIG. 3



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FIG. 5

- continuation -

HBV DNA		1730		1760
Pt	pg/ml	CTGGGAGGAG	TTGGGGGAGG	AGATTAGGTT AAAGGTA
p=0.0001				
40	5	-----	-----	---G---
31	4	-----	-----	---A---A---T-A-
42	4	G-----	-----C---	---GC---
44	3	G-----	-----	---AG---
32	3	G-----	-----T---	---G---
47	3	-----	-----	---A---C---
49	2	-----	-----	---A---AC
50	2	-----	-----	---A---
52	2	-----	-----	---G---
53	2	-----	-----	---G---
54	2	G-----	-----	---G---
56	2	-----	-----	---G---
60	1	-----	-----	---A---
61	1	-----	-----	---G---
62	1	-----	-----	---G---
33	1	-----	-----	---G---
65	1	-----	-----	---G---
67	0.8	-----	-----	---A---
68	0.8	-----	-----	---T---
69	0.6	G-----	-----	---G---
72	0.6	-----	-----	---A---T---
73	0.6	-----	-----	---G---
74	0.5	-----	-----	---A---
75	0.5	G-----	-----	---G---
76	0.5	G-----	-----	---G---
77	0.4	-----	-----	---G---
78	0.4	G-----T---	-----	---G---T-A-
79	0.3	-----	-----	---G---
80	0.2	-----	-----	---G---
81	0.1	-----	-----	---AC---
82	0.1	-----	-----	---G---
83	0.1	-----GA-GA	-----	---G---
84	0.1	-----	-----	---G---
85	0.1	-----	-----	---G---
86	0.1	-----	-----	---G---
87	0.1	G-----	-----	---G---

FIG. 6

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1687

GAC CGACCTTGAG GCATACTTCA AAGACTGTTT GTTTAAAGAC TGGGAGGAGT

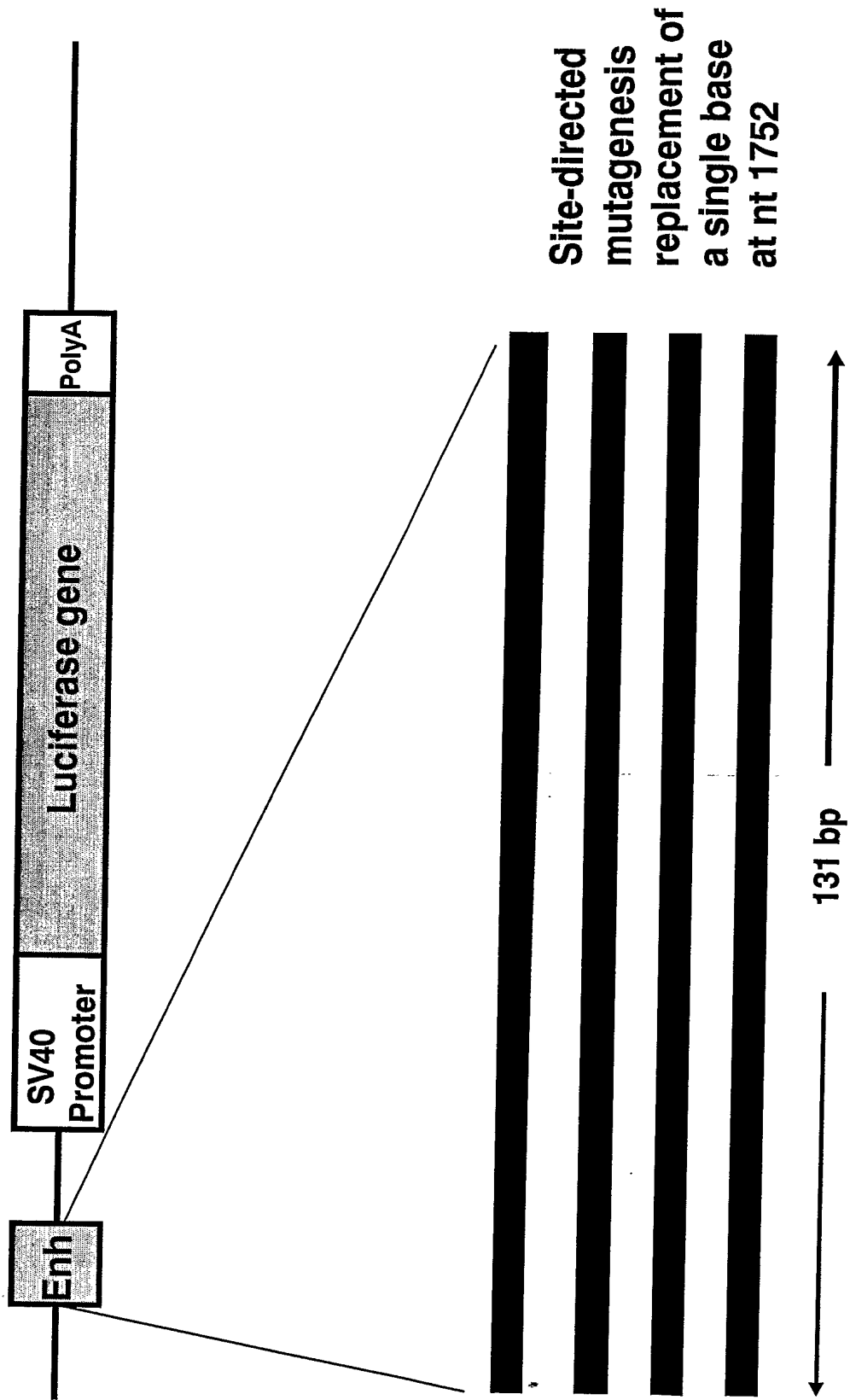
1741

TGGGGGAGGA GATTAGGTTA AAGGTCTTTG TACTAGGAGG CTGTAGGCAT AAATTGGTCT

1801

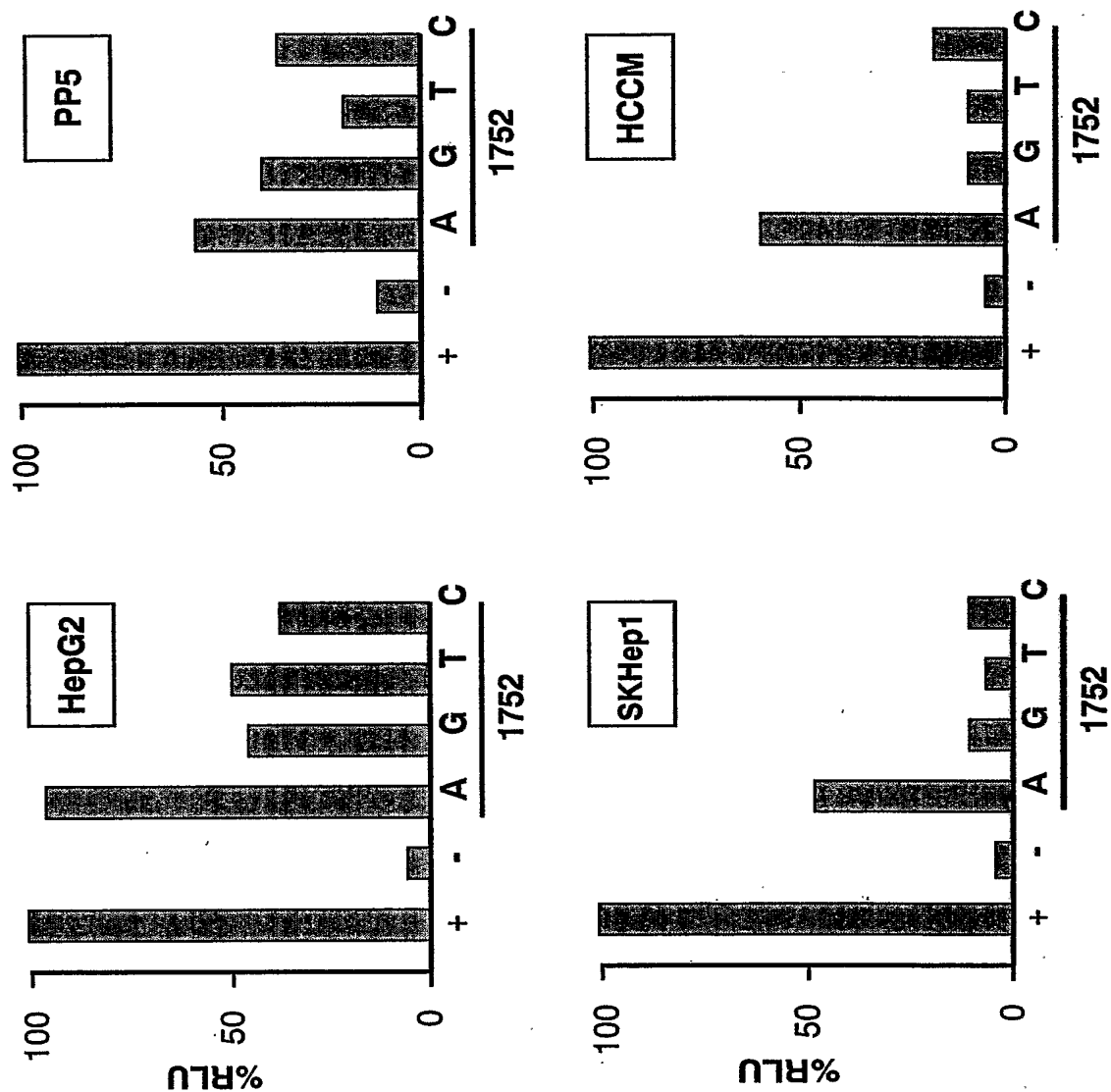
GTTCA

FIG. 7



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FIG. 8



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FIG. 9

hnRNPk variant 2

M E T E Q P E E T F P N T E T N G E F G K R P A E D M 22
 atggaactgaacagccagagaacaccttccctaactgaaaccaatggtgaatttggtaaacgccctgcagaagatatg
 E E E Q A F K R S R N T D E M V E L R I L L Q S K N A 44
 gaagaggaacaagcatttaaaagatctagaaacactgatgagatggttgaattacgcattctgcttcagagcaagaatgct
 G A V I G K G K N I K A L R T D Y N A S V S V P D S 66
 ggggcagtgattggaaaaaggaggcaagaatatattaaggctctccgtacagactacaatgccagtggtttcagtcaccagacagc
 S G P E R I L S I S A D I E T I G E I L K K I I P T L 88
 agtggccccgagcgcatattgagtatcagtgctgatattgaaacaattggagaaaattctgaagaaaaatcatccctaccttg
 E E G L Q L P S P T A T S Q L P L E S D A V E C L N Y 110
 gaagagggcctgcagttgccatcacccactgcaaccagccagctcccgctcgaatctgatgtgtggaatgcttaaatatc
 Q H Y L G S D F D C E L R L L I H Q S L A G G I I G V 132
 caacactataaagggaagtgacttttgactgcgagttgaggctgttgattcatcagagtcagcaggaggaattattggggtc
 K G A K I K E L R E N T Q T T I K L F Q E C C P H S T 154
 aaagtgctaaaaattaaagaacttcgagagaaacactcaaacaccatcaagcttttccagggaatgctgtcctcattccact
 D R V V L I G G K P D R V V E C I K I I L D L I S E S 176
 gacagagttgttcttattggaggaaaacccgatatagggtttagagtgcatataagatcatccttgatcttatatctgagtct
 P I K G R A Q P Y D P N F Y D E T Y D Y G G F T M M F 198
 cccatcaaggacgtgcacagccttatgatcccaatttttacgatgaaacctatgattatggtggtttttacaatgatgttt

KH 1

KH 2

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FIG. 9

hnRNPk variant 3

M E T E Q P E E T F P N T E T N G E F G K R P A E D M
 atggaaactgaacagccagaagaaccttccctaactgaaaccaatggtgaatttggtaaacgccctgcagaagatag 22
 E E E Q A F K R S R N T D E M V E L R I L L Q S K N A
 gaagaggaacaagcatttaaaagatctagaacaactgatgagatgggttgaaattacgcattctgcttcagagcaagaatgct 44
 G A V I G K G G K N I K A L R T D Y N A S V S V P D S
 ggggcagtgattggaaaaggaggcaagaatatattaaggctctccgtacagactacaatgccagtggtttcagtcaccagacagc 66
 S G P E R I L S I S A D I E T I G E I L K I I P T L
 agtggcccgagcgcatattgagtgatcagtgctgatatgaaacaattggagaaaattctgaagaaaatcatccctaccttg 88
 E E G L Q L P S P T A T S Q L P L E S D A V E C L N Y 110
 gaagagggcctgcagttgccatcacccactgcaaccagccagctcccgctcgaatctgatgctgtggaatgcttaaatatc
 Q H Y L G S D F D C E L R L L I H Q S L A G G I I G V 132
 caacactataaaggaaagtgaactttgactgcgagttgaggctgttgattcatcagagctctagcaggaggaattattggggtc
 K G A K I K E L R E N T Q T T I K L F Q E C C P H S T 154
 aaagtgctaaaattaaagaacttcgagagaacactcaaacaccatcaagcttttccaggaatgctgtcctcattccact
 D R V V L I G G K P D R V V E C I K I I L D L I S E S 176
 gacagagttgttcttatttgaggagaaaaccgcataggggttgtagagtgcataaagatcatccttgatcttatatctgagtc
 P I K G R A Q P Y D P N F Y D E T Y D Y G G F T M M F 198
 cccatcaaaggacgtgcacagccttatgatcccaatttttacgatgaaaccctatgattatgggtgttttacaatgatgttt

KH 1

KH 2

FIG. 9

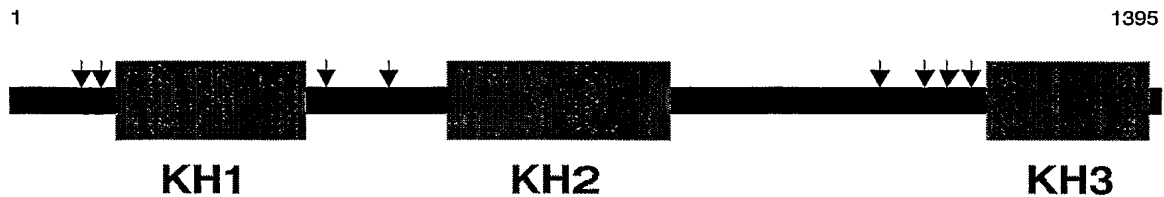
hnRNPK variant 3 (continued)

D D R R G R P V G F P M R G R G G F D R M P P G R G G 220
 gatgaccgtcgcggacgccagtggtggttcccatgcgggaagagtggttttgacagaatgcctcctggtcgggtggg
 R P M P P S R R D Y D D M S P R R G P P P P P P P G R G 242
 cgtcccatgcctccatctagaagagattatgatgatagagccctcgtcgaggaccacctccccctcctcccgacgagcc
 G R G G S R A R N L P P P P P P R G G D L M A Y D 264
 ggccgggtggtagcagagctcggaatcttctctccaccaccaccacctagaggggagaccctcatggcctatgac
 R R G R P G D R Y D G M V G F S A D E T W D S A I D T 286
 agaagaggagacctggagaccgttacgcggcatggttggttcagtgctgatgaaacttgggactctgcaatagataca
 W S P S E W Q M A Y E P Q G G S G Y D Y S Y A G R G 308
 tggagcccatcagaatggcagatggcttatgaaccacaggggtggctccggatatgattattcctatgcaggggtcgtggc
 S Y G D L G G P I I T T Q V T I P K D L A G S I I G K 330
 tcatatggtgatcttggtagcctattattactacacaagtaactattcccaaagatttggctggatctattattggc
 G G Q R I K Q I R H E S G A S I K I D E P L E G S E D 352
 ggtggtcagcggattaaacaaatccgtcatgagtcgggagcttcgatcaaaattgatgagccttttagaaggatccgaagat
 R I I T I T G T Q D Q I Q N A Q Y L L Q N S V K Q Y A 374
 cggatcattaccattacagggaacacagcagacagatacagaatgcacagtatttgcgcagaacagtgagaagcagtatgca
D V E G F * 379
 gatgttgaaggattcttaa

KH 3

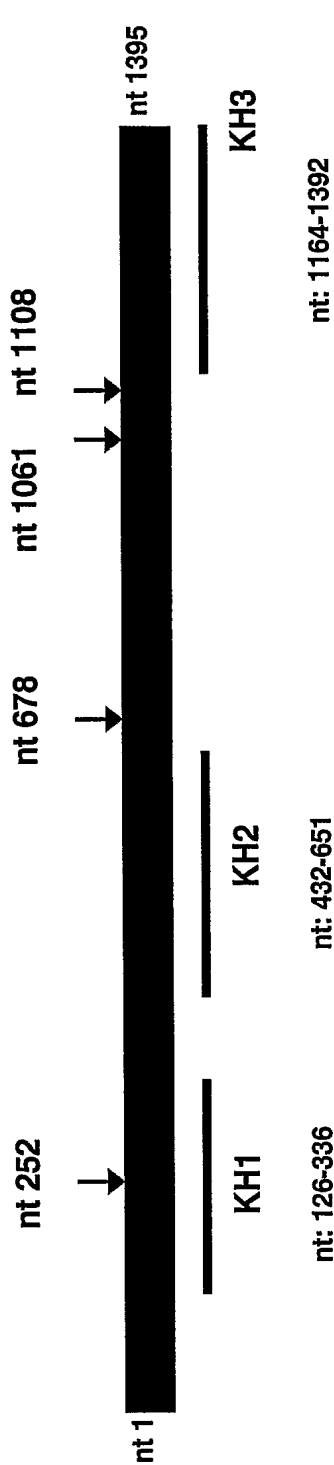
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FIG. 10



Subjects	Location	Mutation	Frequency	Variant
1	90A>G	Silent	1	V3
	112A>G	Asn > Asp	1	
	160G>A	Ala > Thr	1	
	215A>G	Tyr > Cys	1	
	1294G>A	Asp > Asn	1	
	1311T>C	Silent	1	
2	143T>C	Leu > Pro	1	V2
	392A>C	Asn > His	1	
3	667C>T	Missense	1	V3
4	734A>C	Asp > Ala	1	V3
8	278A>T	Asp > Val	1	V3
	469G>C	Gly > Arg	1	
	1252G>A	Gly > Arg	1	
9	252C>T	Silent	2	V3
	1242T>C	Silent	1	
10	252C>T	Silent	2	V3
	324G>T	Leu > Phe	1	
	722T>C	Met > Thr	1	
11	664G>A	Ala > Thr	1	V3
	1108 to 1122	Deletion	2	
	1147C>G	Pro > Gly	1	
	1174G>A	Val > Ile	1	
12	1108 to 1122	Deletion	2	V2
	1216G>T	Gly > Cys	1	
13	685T>C	Phe > Leu	1	V2
	731A>T	Asp > Val	1	
	756A>C	Silent	1	
	780T>C	Silent	1	
	1067A>T	Glu > Va	1	

FIG. 11

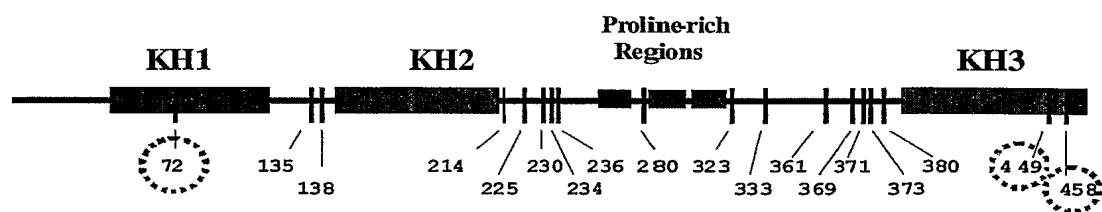


Location (nt)	AA change	Frequency	Source
252C>T	Silent	2 samples	this study
678C>T	Pro>Ser	not validated	dbSNP:11548847
1061A>C	Pro>Gln	not validated	dbSNP:11548850
1108 to 1122	Deletion	2 samples	this study

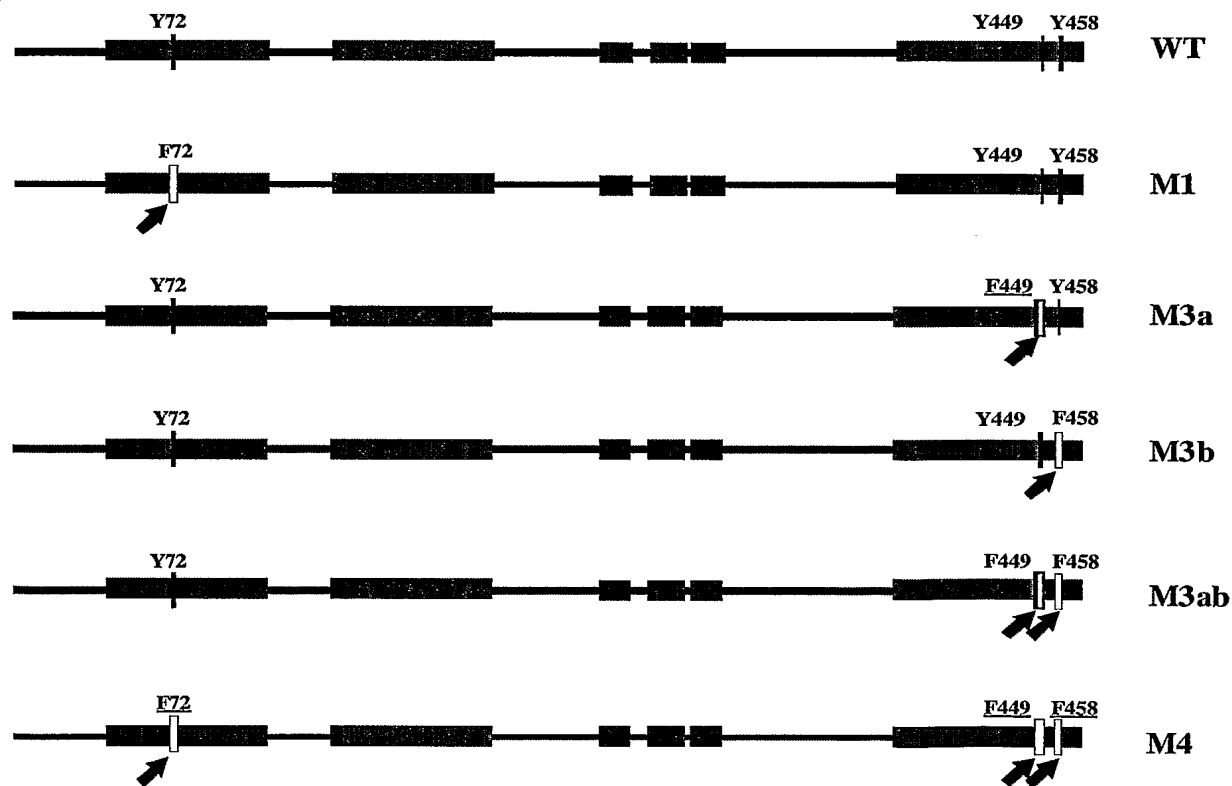
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FIG. 13

A

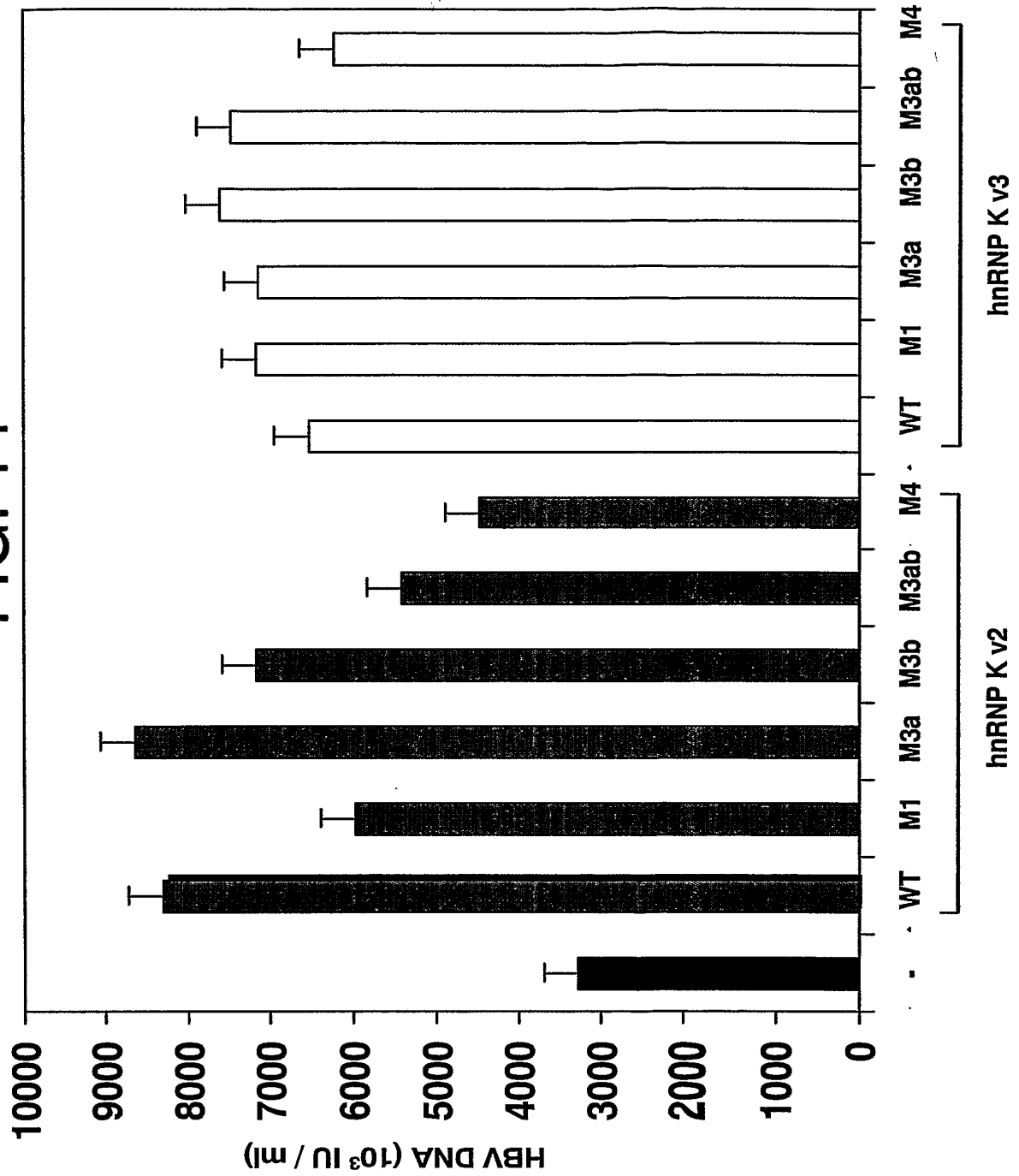


B



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FIG. 14



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FIG. 15

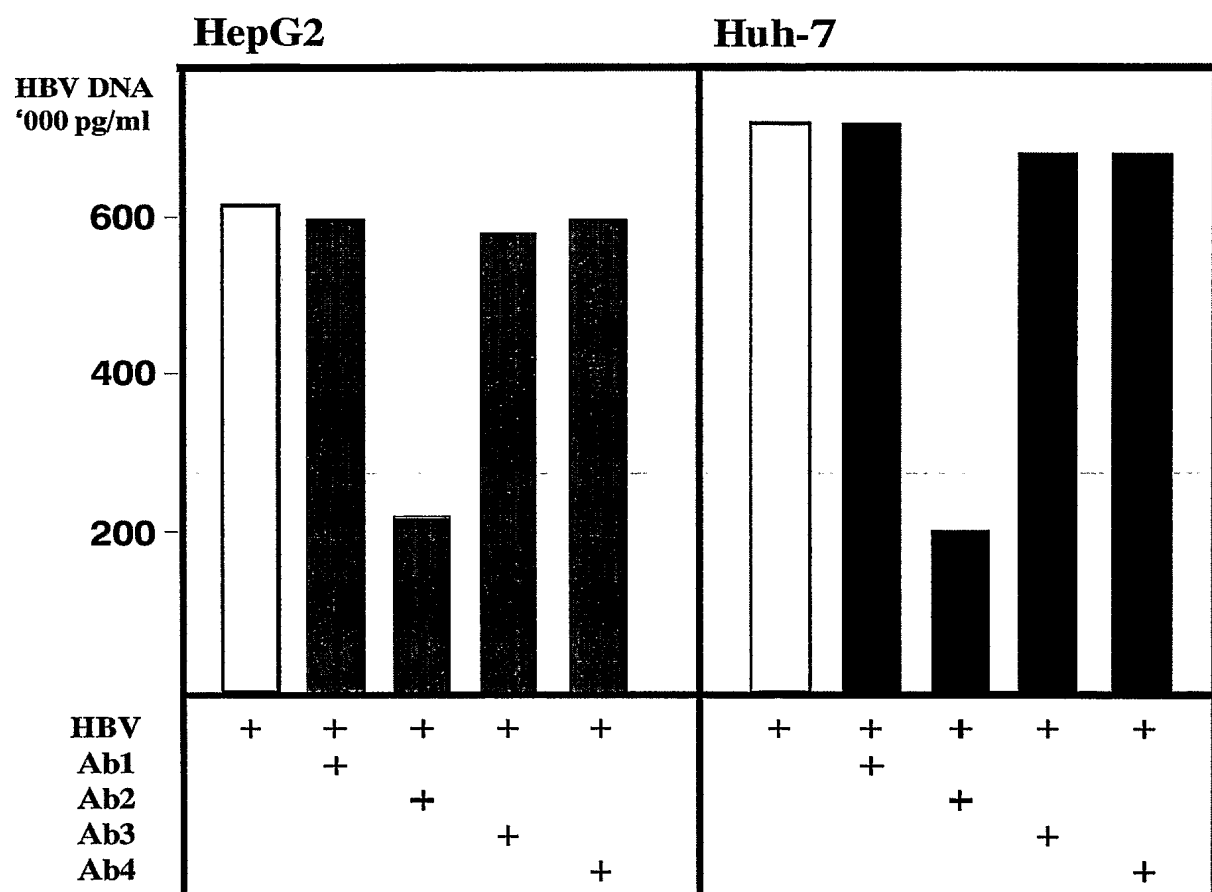
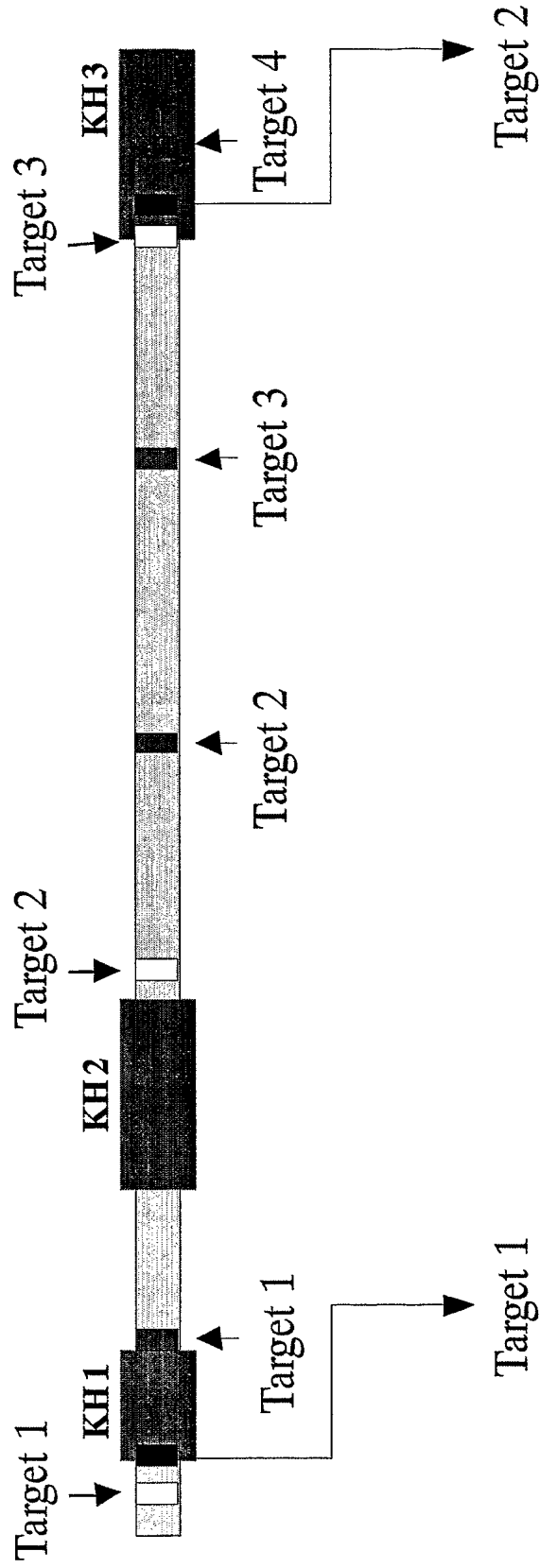


FIG. 16

Selection of RNAi target sequences

➤ Three sources: ■ Source A ■ Source B □ Source C



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FIG. 17

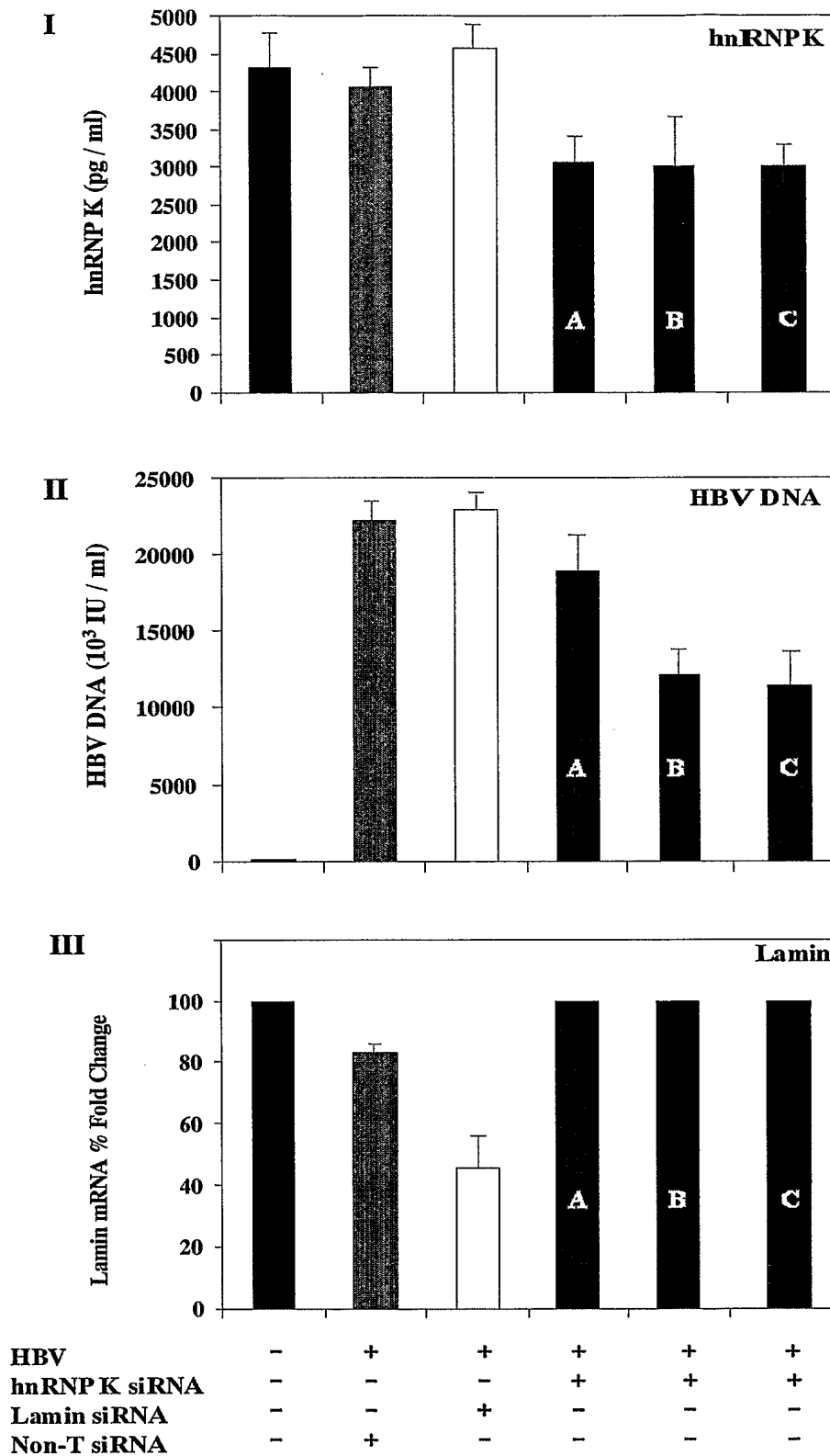


FIG. 18

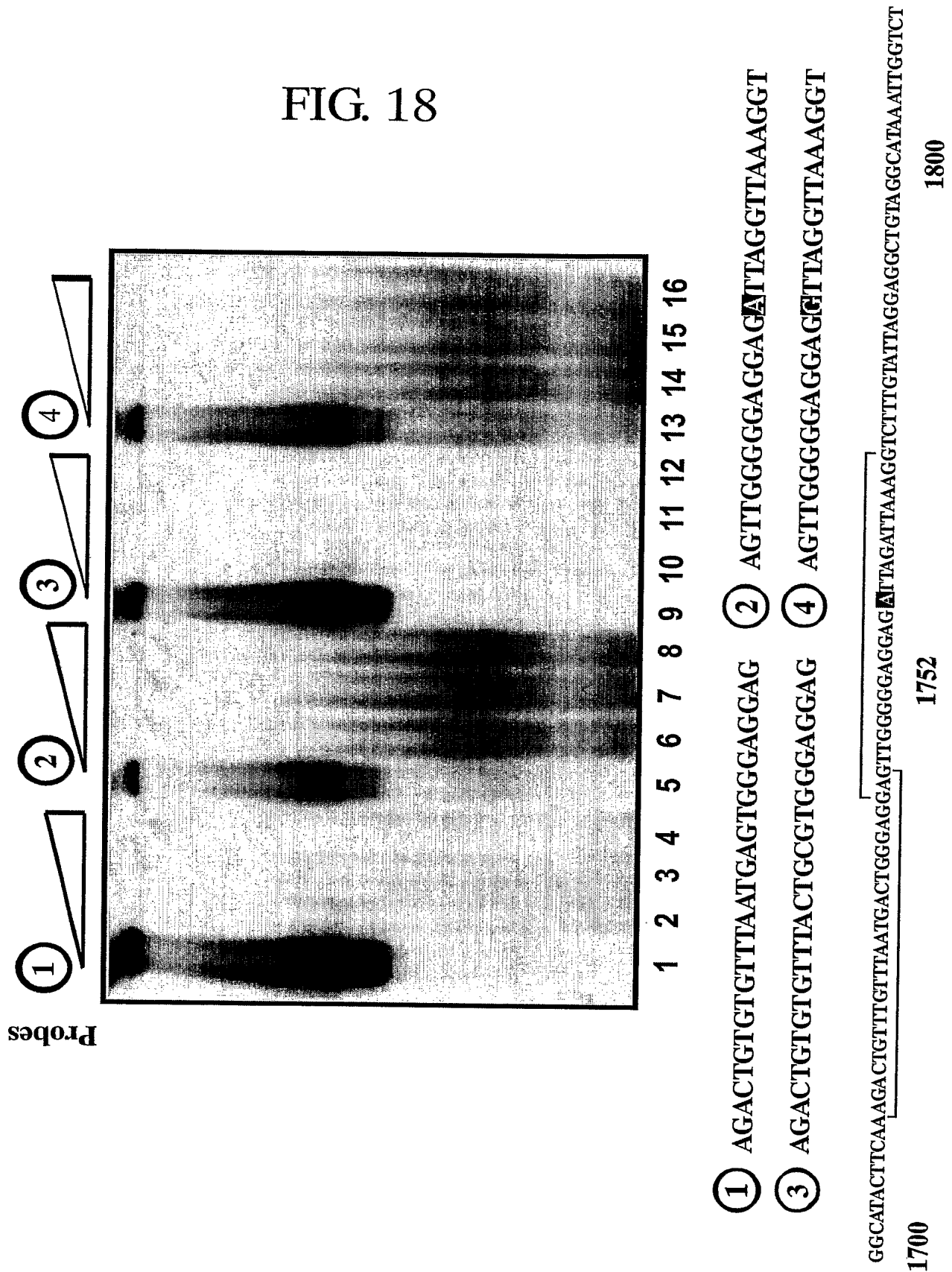
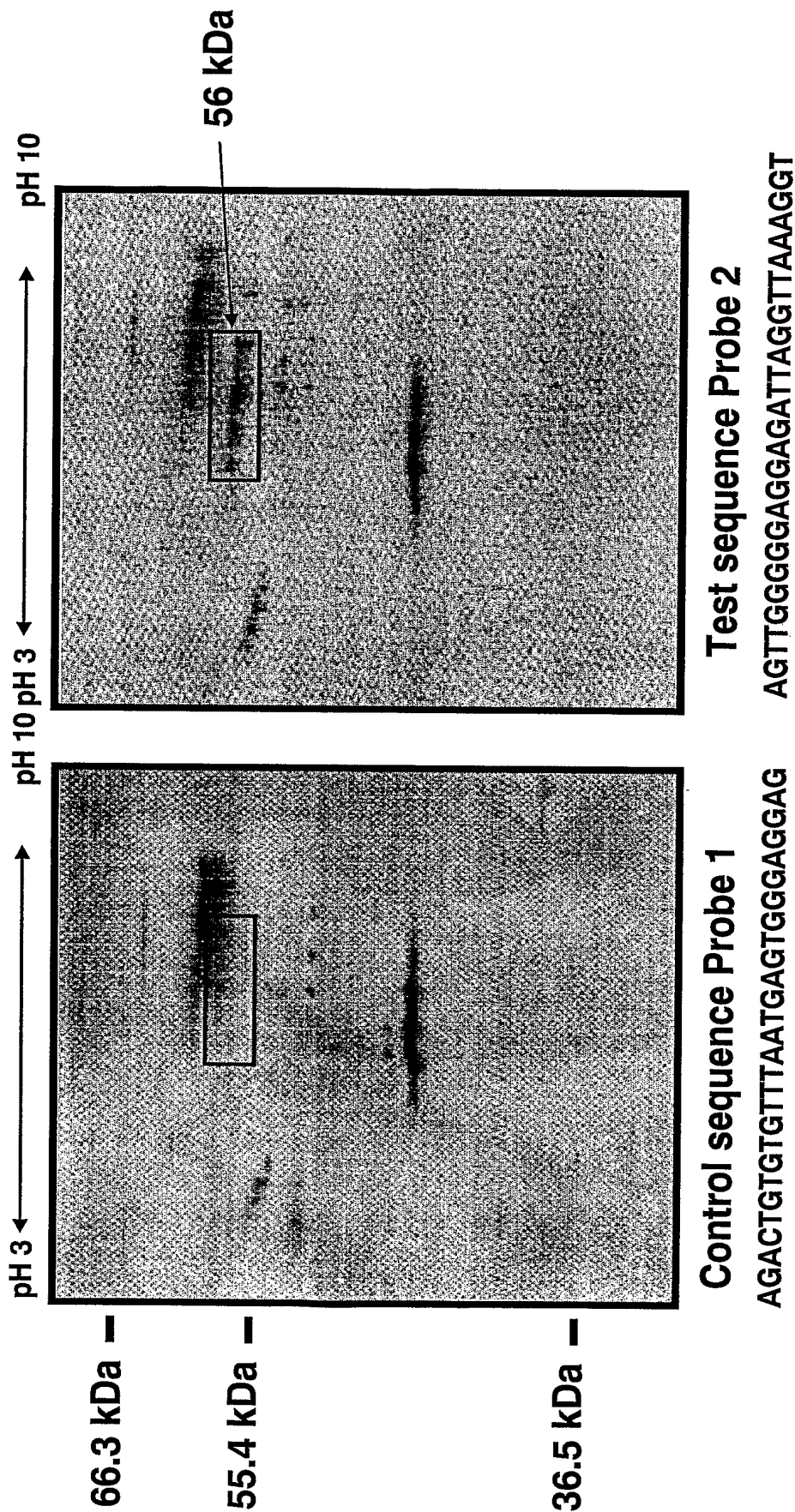


FIG. 19



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FIG. 20

Mass: 48708 Total score: 607 Peptides matched: 21

Query	Observed	Mr(expt)	Mr(Calc)	Score	Peptide
3	437.2488	872.4821	872.4967	16	DLAGSIIGK
5	499.2279	996.4402	996.4334	44	GGDLMAYDR
8	351.8774	1052.6088	1052.6088	33	VVLIGGKPDR
9	549.7244	1097.4332	1097.4573	27	GSDFDCELR
10	553.7588	1105.5019	1105.5073	55	NTDEMVELR
11	385.1795	1152.5150	1152.5345	39	GGDLMAYDRR
12	390.5085	1168.5021	1168.5294	(19)	GGDLMAYDRR
13	597.8453	1193.6749	1193.6920	29	NLPLPPPPPPR
14	597.8495	1193.6833	1193.6920	(18)	NLPLPPPPPPR
15	597.8527	1193.6898	1193.6920	(24)	NLPLPPPPPPR
16	630.2869	1258.5582	1258.5677	60	IDEPLEGSEDR
17	670.8989	1339.7822	1339.7962	88	IILDLISESPIK
18	450.5459	1348.6142	1348.6405	45	SRNTDEMVELR
21	506.9706	1517.8884	1517.9293	18	LLIHQSLAGGIIGVK
22	511.9268	1532.7569	1532.7874	22	IIPITLEEYQHYK
24	517.2101	1548.6068	1548.6701	16	LFQECPPHSTDR
25	518.6332	1552.8761	1552.9188	16	IILDLISESPIKGR
27	579.2644	1734.7697	1734.7995	15	RPAEDMEEEQAFKR
28	594.2626	1779.7642	1779.7911	(12)	TDYNASVSVDPSSGPER
29	890.9033	1779.7910	1779.7911	62	TDYNASVSVDPSSGPER
33	707.6703	2119.9874	2120.0134	23	ALRTDYNASVSVDPSSG

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FIG. 21

hnRNPK variant 2
 hnRNPK variant 3
 HBV-binding protein

METEQPEETFPNTETNGEFK RPAEDMEEHQAFKRSRNTDEMVELR ILLQSKNAGAVICKGGKNIK ALRTDYNASVSPD⁸⁰
 METEQPEETFPNTETNGEFK RPAEDMEEHQAFKRSRNTDEMVELR ILLQSKNAGAVICKGGKNIK ALRTDYNASVSPD⁸⁰
 RPAEDMEEHQAFKRSRNTDEMVELR

hnRNPK variant 2
 hnRNPK variant 3
 HBV-binding protein

SSG PERILSADIETIGEILKKIIPITLLEGLQLPSPTATSQLPLESDAVECLNYQHYK GSDFDCELRLLIHQSLAGGII¹⁶⁰
 SSG PERILSADIETIGEILKKIIPITLLEGLQLPSPTATSQLPLESDAVECLNYQHYK GSDFDCELRLLIHQSLAGGII¹⁶⁰
 SSG

hnRNPK variant 2
 hnRNPK variant 3
 HBV-binding protein

GVK GAKIKELRENTQTNIK LFQECCHSTDRVVLIGGKPDV VVECIK IILDLISESPKGR AQPYPDPNFYDETYDYGFT²⁴⁰
 GVK GAKIKELRENTQTNIK LFQECCHSTDRVVLIGGKPDV VVECIK IILDLISESPKGR AQPYPDPNFYDETYDYGFT²⁴⁰
 GVK LFQECCHSTDRVVLIGGKPDV IILDLISESPKGR

hnRNPK variant 2
 hnRNPK variant 3
 HBV-binding protein

MMFDDRRGRPVGFPMRGRGGFDRMP PGRGGRMP PRRDDYDDMSPRRGGPPPPPPGRGGSRR NLPLPPPPPPPRGGDLMA³²⁰
 MMFDDRRGRPVGFPMRGRGGFDRMP PGRGGRMP PRRDDYDDMSPRRGGPPPPPPGRGGSRR NLPLPPPPPPPRGGDLMA³²⁰
 NLPLPPPPPPPRGGDLMA

hnRNPK variant 2
 hnRNPK variant 3
 HBV-binding protein

YDRR GRPGDRYDGMVGFSADETWD SAIDTWSFSEWQAYEPQGGSGDYSYAGGRSGYDGLGGPIITTTQVTIPKDLAGSI⁴⁰⁰
 YDRR GRPGDRYDGMVGFSADETWD SAIDTWSFSEWQAYEPQGGSGDYSYAGGRSGYDGLGGPIITTTQVTIPKDLAGSI⁴⁰⁰
 YDRR

hnRNPK variant 2
 hnRNPK variant 3
 HBV-binding protein

IGKGGQRIKQIRHEGASIK IDEPLEGSEDR IITITGTQDQIQNAQYLLQNSVKQYSGKFF⁴⁶⁰
 IGKGGQRIKQIRHEGASIK IDEPLEGSEDR IITITGTQDQIQNAQYLLQNSVKQYADVEGF⁴⁶¹
 IDEPLEGSEDR